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Role of Ferric Citrate in Correcting Anemia Among Chronic Kidney Disease Patients on Maintenance Hemodialysis

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Abstract

Background: In chronic kidney disease (CKD), anemia and hyperphosphatemia are significant complications. Anemia due to erythropoietin and iron deficiencies, often requires supplementation. Phosphate binders including ferric citrate, sevelamer carbonate, and calcium acetate are crucial for managing hyperphosphatemia, as they prevent the absorption of dietary phosphate.

Objective: Present study was aimed to assess the role of ferric citrate in correcting anemia among CKD patients on maintenance hemodialysis (MHD).

Methods: This randomized control trial was carried out at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, that enrolled 45 adult CKD patients on hemodialysis. Study population were divided into equal three groups to compare the effects of ferric citrate, sevelamer carbonate, and calcium acetate. Of these groups, ferric citrate was the intervention group, whereas sevelamer carbonate and calcium acetate were the active control group. Data were collected through interviews and medical evaluations, including serum hemoglobin level and iron status. The focus was on the role of ferric citrate in correcting anemia and iron status among maintenance hemodialysis (MHD) patients.

Results: In this study with CKD patients undergoing hemodialysis, the majority of participants were male across all groups. Initially, no significant differences were observed in serum hemoglobin, iron, and transferrin saturation (TSAT) level among the groups. However, after three months of treatment, significant ($p<0.05$) improvements were noted in the intervention group, with increases in hemoglobin level from 9.39 ± 1.08 g/dl to 10.6 ± 0.89 g/dl and in serum iron level from 50.8 ± 17.0 µg/dl to 118.2 ± 35.5 µg/dl. Transferrin saturation was also raised significantly from 23.5% to 45%. In contrast, the control groups did not show significant changes in these parameters. Ferric citrate significantly ($p<0.05$) increases serum ferritin level from 344 ng/ml to 568 ng/ml. No significant changes were noted in total iron binding capacity (TIBC) level across all phosphate binders.

Conclusion: The study indicates that ferric citrate is better at correcting hemoglobin level and iron status in CKD patients on MHD than sevelamer carbonate and calcium acetate. Therefore, ferric citrate can be used as a primary treatment for the correction of anemia in MHD patients.

Keywords: Anemia; Chronic Kidney Disease (CKD); Hyperphosphatemia; Maintenance Hemodialysis (MHD); Phosphate Binders.

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Introduction

Chronic kidney disease (CKD) is a prevalent non-communicable condition that causes significant physical suffering and imposes socio-economic and psychological burdens on patients [1]. It encompasses various disorders that persistently impair kidney structure and function [2]. Patients with CKD often suffer from hyperphosphatemia and anemia, which elevate their risk of cardiovascular diseases and contribute to overall morbidity and mortality [3]. Phosphate absorption primarily occurs in the jejunum and ileum, with 60% being actively absorbed through sodium-phosphate co-transporters [4, 5]. Phosphate binders can reduce this absorption rate up to 40%. During renal impairment homeostatic mechanisms to maintain phosphate level fails, leading to hyperphosphatemia [6, 7].

Anemia frequently occurs in the advanced stages of CKD [8]. Its development is primarily due to a lack of erythropoietin, a hormone produced by the kidneys, and iron deficiency. Patients with CKD often need extra iron, especially those on hemodialysis, typically administered through infusion, as they cannot effectively use their body's iron reserves. Patients undergoing renal replacement therapy often face the dual challenge of hyperphosphatemia and iron deficiency, necessitating the use of phosphate binders and iron supplements. Treating these conditions can be difficult due to the limited effectiveness of available drugs, along with their side effects and poor treatment compliance [9]. Proper management of anemia, iron deficiency, and hyperphosphatemia is crucial to reduce the risk of death and improve the quality of life for patients with advanced CKD [10, 11].

Dialysis treatments, even when paired with dietary restrictions on phosphate, are typically insufficient in managing hyperphosphatemia [12]. As a result, most dialysis patients require phosphate binders to help eliminate dietary phosphate from the body. These binders include calcium-based options, non-absorbable polymers, and heavy metal salts [13. 14]. While calcium-based binders can lower serum phosphate levels, they often necessitate larger doses for full efficacy, causing more side effects [15]. Sevelamer is a non-absorbable, synthetic polymer that binds phosphate, preventing its absorption [16]. It's as effective as calcium-based binders but more expensive and may cause gastrointestinal side effects. However, it reduces the risk of hypercalcemia compared to calcium-based options [17].

Iron-based phosphate binder like ferric citrate is used to simultaneously manage hyperphosphatemia and iron deficiency anemia [9, 18]. Ferric citrate not only effectively lowers serum phosphate levels but also serves as an iron supplement, potentially reducing the need for iron infusions and the dosage of erythropoiesis-stimulating agents (ESA) in CKD patients. Even at low doses, ferric citrate can improve iron stores and decrease the ESA dosage required for treating anemia in CKD patients [19].

In CKD patients reduced iron or hemoglobin and elevated phosphate level can cause a range of symptoms and complications. Conversely, it's also important to note that excessively high hemoglobin or iron level and abnormally low phosphate level can have severe adverse effects [20]. While sevelamer carbonate and calcium acetate has been in use for maintaining phosphate level among CKD patients, data on the effects of ferric citrate on maintaining phosphate level and constitutively correcting anemia is scarce, especially in the perspective of Bangladeshi population. Present study aimed at assessing the role of ferric citrate in correcting anemia among CKD patients on maintenance hemodialysis.

Materials & Methodology

This randomized controlled trial was conducted at Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from July 2022 to March 2023. Following the established criteria, a total of 45 adult (age>18 years) patients with chronic kidney disease (CKD) who were receiving hemodialysis were selected by purposive sampling technique. Patients who had ferritin levels above 1000 ng/ml, TSAT over 50%, hemoglobin levels below 8 gm/dl or above 12 gm/dl were excluded. Additionally, patients with anemia not related to CKD, those with active gastrointestinal diseases (e.g., peptic ulcer disease, chronic ulcerative colitis, previous gastrectomy or duodenectomy), active malignancy, pregnancy, lactation, or known intolerance to ferric citrate, sevelamer carbonate, or calcium acetate, were also excluded from the study. All participants were subjected to comprehensive medical history reviews, physical assessments, and relevant investigations. The study patients who fit the selection criteria were randomly assigned into three groups, with 15 participants in each. One group was treated with ferric citrate (Group A), while the other two groups received sevelamer carbonate (Group B) and calcium acetate (Group C), respectively (Table- 1). Follow-ups were scheduled every seven days to monitor medication adherence. For each participant, evaluations were conducted to measure levels of serum hemoglobin, serum iron, transferrin saturation percentage, serum ferritin, and total iron binding capacity (TIBC). Outcome variables were compared between baseline with that of 3 months after starting treatment.

Statistical analysis of data

After collection, all data were checked and compiled. Statistical analysis was performed using a windows-based software program Statistical Packages for Social Sciences (SPSS) version- 25. Quantitative data were expressed as mean with standard deviation (SD) and qualitative data

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Table 1: Dosage and route of drugs administration

Drugs	Doses	Route	Frequency	Duration
Ferric citrate	420 mg	Oral	Thrice daily	3 months
Sevelamer carbonate	800 mg	Oral	Thrice daily	3 months
Calcium acetate	667mg	Oral	Thrice daily	3 months

were expressed as frequency with percentage. To determine statistical significance, one-way ANOVA test/Kruskal-Wallis test, Paired t-test/Wilcoxon test were considered according to applicability. A p value <0.05 was considered as statistically significant.

Results

This study was intended to assess the role of ferric citrate in correcting anemia among CKD patients on maintenance hemodialysis. The mean(±SD) age was 49.3±13.5 years in group A, that was 53.7±12.3 years and 54.3±12.9 years respectively in group B and group C. Study population was predominantly male; 53.3%, 53.3% and 66.7% male in group A, B and C respectively (Figure 1).

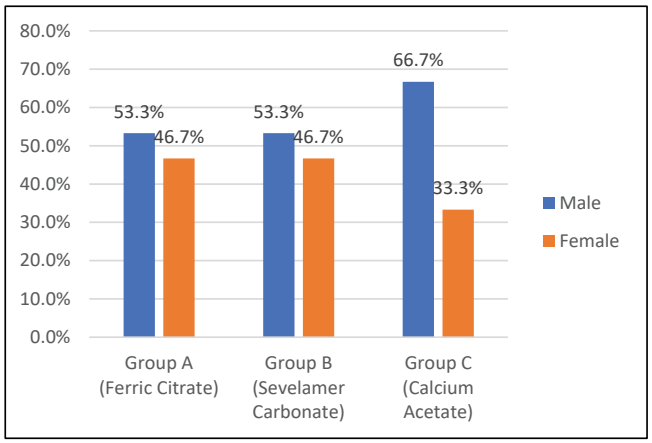

Figure 1: Gender distribution in study groups (N= 45)

At baseline there was no statistically significant difference in the serum hemoglobin level, serum iron level and transferrin saturation (%) among the study groups. After 3 months of treatment with phosphate binders, there were statistically significant (p<0.05) difference was observed among the study groups for serum hemoglobin level, serum iron level and transferrin saturation (%). At baseline there was no statistically significant difference in the median values (IQR) of TIBC and serum ferritin levels among study groups, but statistically significant (p<0.05) difference was noted in the median value of serum ferritin after 3 months of phosphate binder treatment (Table- 2)

It was observed that, there was no statistically significant difference in the hemoglobin level at baseline and after 3 months in patients taking calcium acetate (p= 0.06) and sevelamer carbonate (p= 0.55). Patients taking ferric citrate had significantly (p<0.05) increased in their hemoglobin level from baseline (9.39 ± 1.08 g/dl) to 3 months after treatment (10.6 ± 0.89 g/dl) (Figure- 2a). There was no statistically significant difference in the serum iron level at baseline and after 3 months in patients taking calcium acetate (p= 0.07) and sevelamer carbonate (p= 0.55). Patients taking ferric citrate had significantly (p<0.05) increased in their iron level from baseline (50.8 ± 17.0 µg/dl) to 3 months after treatment (118.2 ± 35.5 µg/dl) (Figure- 2b). The transferrin saturation was significantly (p<0.05) increased from 23.5% to 45% in patient taking ferric citrate from baseline to 3 months after treatment (Figure- 2c). No statistically significant change in transferrin saturation (%) was observed for patients taking calcium acetate (p= 0.09) and sevelamer carbonate (p= 0.07).

Table 2: Hematological parameters of the study population (N= 45)

Variables		Group A (n = 15)	Group B (n = 15)	Group C (n = 15)	p value
Hemoglobin (g/dl)	At baseline	9.39 ± 1.08	9.79 ± 0.96	9.51 ± 0.86	0.51*
	After 3 months	10.6 ± 0.89	10 ± 0.75	9.27 ± 0.51	<0.05*
Serum iron (µg/dl)	At baseline	50.8 ± 17.0	57.9 ± 18.5	63.4 ± 23.5	0.83*
	After 3 months	118.2 ± 35.5	60.7 ± 29.4	66.1 ± 23.9	<0.05*
Transferrin Saturation (%)	At baseline	23.5 (20 - 30)	22 (18.4 - 28)	24 (19.9 - 28)	0.71**
Median (IQR)	After 3 months	45 (42.8 - 48)	23 (19 - 25)	21(20 - 34.6)	<0.05**
TIBC (µg/dl)	At baseline	220 (190 - 250)	252 (232 - 280)	240 (217 - 260)	0.15**
Median (IQR)	After 3 months	240 (210 - 293)	240 (220 - 280)	253 (222 - 280)	0.99**
Serum Ferritin (ng/ml)	At baseline	344 (219 - 469)	300 (269 - 364)	310 (219 - 400)	0.70**
Median (IQR)	After 3 months	568 (413 - 740)	320 (230 - 409)	310 (230 - 415)	<0.05**

Data presented as mean ± SD, Median (IQR), Group A: Ferric Citrate, Group B: Sevelamer Carbonate, Group C: Calcium Acetate. *One-way ANOVA was used, **Kruskal-Wallis test was performed

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There was no statistically significant difference in the serum ferritin level at baseline and after 3 months in patients taking calcium acetate (p= 0.07) and sevelamer carbonate (p= 0.12). Patients taking ferric citrate had significant (p< 0.05) increase in their serum ferritin level from baseline 344 ng/ml to 3 months after treatment 568 ng/ml (Figure- 2d). There was no statistically significant difference in the serum TIBC level at baseline and after 3 months in patients taking phosphate binders calcium acetate (p= 0.48), ferric citrate (p= 0.19) and sevelamer carbonate (p= 0.76) (Figure- 2e).

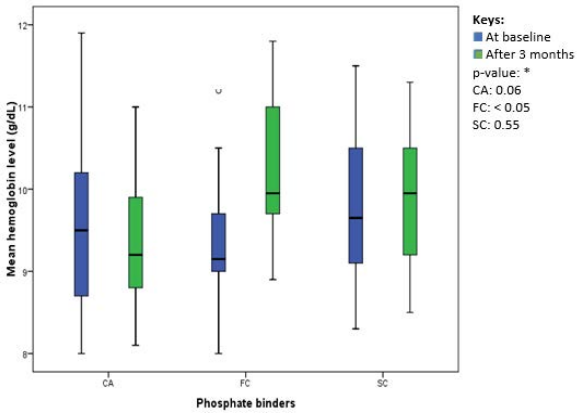

Figure 2a: Changes in hemoglobin level

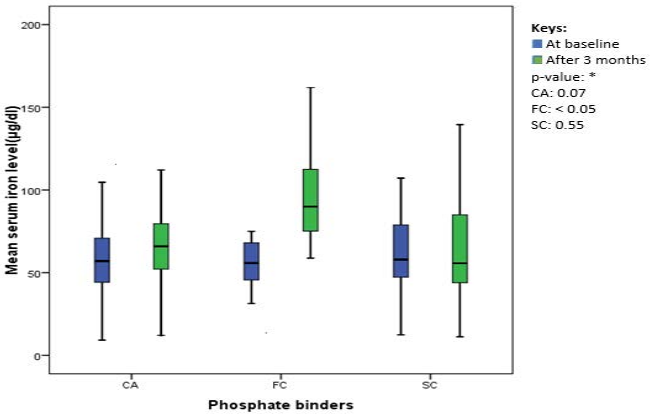

Figure 2b: Changes in serum iron level

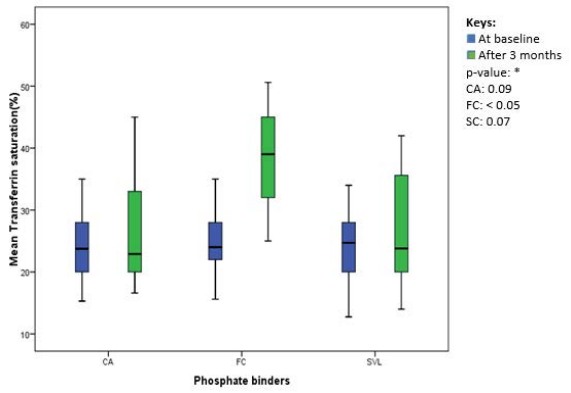

Figure 2c: Changes in transferrin saturation (%)

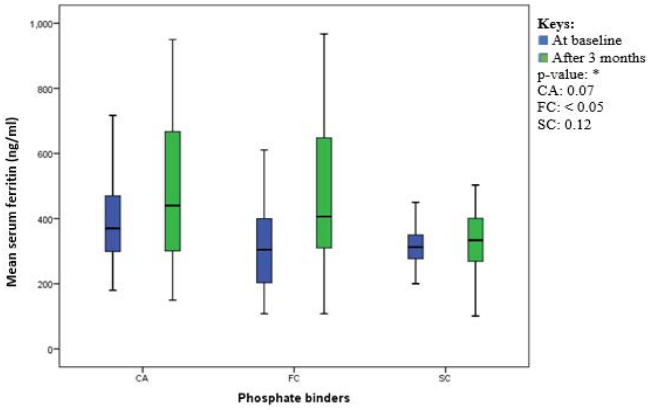

Figure 2d: Changes in serum ferritin level

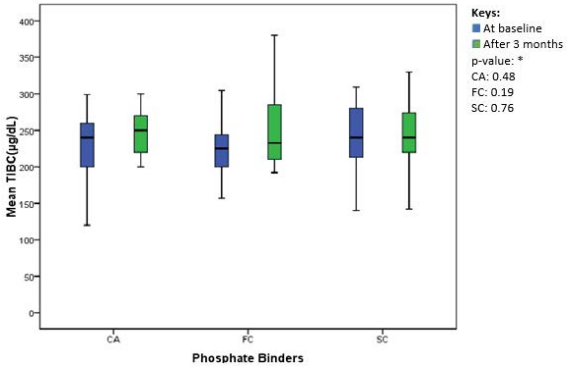

Figure 2e: Changes in TIBC level

Figure 2: Changes in hematological parameters of the study population before and after 3 months treatment with phosphate binders (2a, 2b, 2c, 2d, 2e)

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Discussion

Hyperphosphatemia often causes secondary hyperparathyroidism and anemia, leading to increased prevalence of mortality and morbidity [21, 22]. Early detection and management of hyperphosphatemia among CKD patients is crucial in achieving good prognosis [12, 23]. Present randomized trial was designed to assess the role of phosphate binder agents in correcting anemia among CKD patients on maintenance hemodialysis. In present study, the mean age of the patients was within their early fifties and male predominance was observed; this finding was comparable with a related previous study, where the mean age of the patients was within 50-60 years range with male preponderance (52.8%) [24].

The reason behind anemia in CKD, typically results from a combination of iron and relative erythropoietin deficit. The two cornerstones for treating the anemia that occurs in dialysis patients are iron supplementation and the use of ESA. Dialysis patients must have adequate iron stores in order to respond to ESA therapy [25, 26]. Patients with end stage renal disease (ESRD) who received oral iron supplements to treat both functional and absolute iron insufficiency were unable to retain sufficient iron reserves [26]. Several studies that used ferrous fumarate and ferrous sulfate, two oral iron formulations, at dosages of up to 200 mg/day of elemental iron failed to demonstrate that patients with ESRD were able to achieve or maintain adequate iron reserves [26]. Nowadays, intravenous (IV) iron is frequently used in ESRD patients. Concern over intravenous (IV) iron use has grown as it circumvents many of the physiological mechanisms that control iron absorption and total iron storage and may increase the risk of infection [26]. Studies have revealed that ferric citrate is an effective oral phosphate binder that increases iron stores, increases hemoglobin concentration and reduces the need for intravenous (IV) iron to support erythropoiesis [26, 27]. In contrast to anemic dialysis patients who typically need ESAs (and additional iron) because of the severity of their erythropoietin insufficiency, patients with non-dialytic CKD have higher relative erythropoietin production [28]. Use of ferric citrate in MHD patients reduces the need for ESAs [26].

Present study showed that taking ferric citrate can significantly ($p<0.05$) increase mean serum hemoglobin level, serum iron level, transferrin saturation (%) and serum ferritin level from baseline to 3 months after treatment. On the other hand, patients taking sevelamer carbonate or calcium acetate did not show any significant change in these parameters from baseline to 3 months after treatment ($p>0.05$). A couple of previous studies have shown that ferric citrate, an iron-based intestinal phosphate binder significantly reduces serum phosphate and increase hemoglobin (Hb), serum iron level, transferrin saturation (%) and ferritin level among CKD patients, which supports present study findings [27, 29-33]. Ferric citrate was also found to be more effective in increasing the hemoglobin and serum iron level compared to sevelamer carbonate or calcium acetate in aforementioned studies, suggesting that iron-based phosphate binders such as ferric citrate can be used as an important agent for phosphate reduction as well as correction of iron deficiency anemia among CKD patients.

Calcium acetate is commonly utilized to address low calcium levels in patients with CKD. It's also believed to mitigate the development of renal bone disease, as well as malnutrition and inflammation in CKD patients on maintenance hemodialysis [34, 35]. However, studies have indicated that non-calcium phosphate binders like ferric citrate and sevelamer carbonate are linked to a lower overall mortality risk in CKD patients compared to calcium-based binders, which are associated with a higher risk of cardiovascular death [36]. In addition to phosphate binding, ferric citrate has demonstrated superior results in managing the hemoglobin and iron levels in dialytic patients than sevelamer carbonate and calcium acetate.

Conclusion

This current study has revealed that ferric citrate significantly increases hemoglobin and elevates serum iron, serum ferritin, and TSAT level compared to sevelamer carbonate and calcium acetate from baseline to after 3 months of treatment in MHD patients. A large multi-center study is needed to assess the effectiveness of ferric citrate further and use it as a first line phosphate binder in managing anemia among CKD patients on maintenance hemodialysis.

Limitations of the Study

It was a single center study with a relatively small sample size. Moreover, long-term follow up might be needed to observe the effectiveness and drawbacks of ferric citrate.

Conflict of interest

All authors stated that they have no conflict of interest regarding this publication.

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